

ended at 113, but claim number 113 was mislabeled as number "103" (see Third Preliminary Amendment; submitted on 6/10/2004).

The Examiner rejected claims 84 and 88 under Section 112, para. 2. It is assumed that the Examiner is not referring the currently pending set of claims in the Third Preliminary Amendment, as claim 84 does not correlate with the comments made. Claim 87 has been amended in view of the rejection and the comments by the Examiner. Claim 90 (which is the only claim relating to "hybridizing" in the pending set) was not amended, as it recites "the ligands *are nucleic acids* capable of hybridizing with one or more analytes." (emphasis added). Accordingly, the rejections should be withdrawn.

The Examiner rejected claims 76-81 and 84-90 under Section 102(e) over Gombinski (US 6,297,062), which relates to:

a method for separating at least one species of biological entities from a sample solution, by contacting the sample with a matrix of magnetic particles formed on a substrate such as a sheet, a gel, etc. The particles in the matrix are coupled to entities capable of specifically binding to the species of biological entities to be separated. [see Abstract]

Further, as set forth in the Summary of the Invention (col. 5, lines 38-53) of Gombinski:

Preferably, the matrix should contain magnetic particles, coupled to several different species of second members of the pair forming groups, for example, to different types of antibodies, wherein all the magnetic particles which are coupled to a specific species of said second member are present in a discrete location in the matrix, which is different than the location of the other magnetic particles. When the sample is contacted with said matrix, and each species of biological entities, (first member of the pair forming group, for example, a specific antigen) binds to its specific second member of the pair forming group (for example its specific antibody) which is present in a discrete location in the matrix. Thus each species of the biological entities is spatially separated, in a discrete location, from the other entities, and due to the magnetic properties of the magnetic particles, each species may be obtained separately.

The Examiner alleges that:

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The particle-attached ligands encoded with a chemical or physical characteristic are equivalent to the magnetic particle-attached biological entities-label. Such magnetic particles-attached biological label is attached to the substrate/matrix. The biological entities are proteins such as monoclonal antibodies or oligonucleotides such as RNA or DNA ...” See Office Action page 5.

It is clear, however, that the claimed “array of *several different particle-attached ligands*, wherein *different ligands are attached to different particles* and said particles have a chemical or physical characteristic *that permits identification of the ligand or ligands attached thereto*” (claim 76; emphasis added) and the “encoded, oligonucleotide-bearing beads” (newly added independent claims 114-117) are not “equivalent” to the magnetic particles of Gombinski, with the attached “biological-entities” labels. Gombinski relates to purification by “separating at least one species of biological entities from a sample solution...” (as noted in the Abstract above), there is no need for encoded particles, and no “teaching” of them, as is clarified by the following passage from Example I (col. 16, lines 34-54):

200 µl from 1 µm diameter superparamagnetic *ferrous oxide particles which were coated with a functional affinity group* (Advanced Magnetics, Inc., USA) were drawn from a 50 mg/ml stock solution and were injected to 3 ml of a 2% aqueous solution of low melting point agarose (A-9414, Sigma Chemical Co., USA) at a temperature of 45° C and mixed for 1 minute by a vortex. The agarose was poured into the casting space and then covered with a 7×7 cm hot glass plate. After a few minutes at 35° C. the gel was allowed to cool and was left at room temperature for at least one hour. During this time the magnetic particles were drawn to the stripped magnet and a stripped matrix of magnetic particles at the bottom layer of the gel was then obtained. The same procedure was repeated with the uniform magnet, whereby a uniformed [sic] matrix of magnetic particles was obtained. [emphasis added]

Accordingly, the Gombinski particles are all coated with the same functional group in order to separate a specific constituent from a sample solution with which the matrix is contacted. If the constituent within the sample binds to the functional group on the particle, the binding event can be detected using a “biological entities-label.” But the

particles are not encoded with a "physical or chemical characteristic" or otherwise. In contrast to the invention, the particles within a uniform matrix or within a discrete location of the substrate all carry the same functional group – the "biological-entities label" merely indicates a binding event. In fact, in the preferred arrangement of the Gombinski matrix comprising magnetic particles coupled to different species, these particles – precisely because they are not encoded by a physical or chemical characteristic – must be spatially separated, in different discrete locations on the substrate. The biological entities label, indicating the binding event, will be the same for all particles. Further, the Gombinski method does not require, and does not disclose, an array, but merely a "stripped matrix of magnetic particles" or a "uniformed [sic] matrix" which generally will not be planar.

The Examiner has rejected claim 83 (it is noted that it should be claim 85) under Section 103(a) over Gombinski in view of Nacamulli et al., which relates to determining the "rate of a biomolecular reaction, such as an enzymatic reaction or an affinity binding reaction ... using electrochemiluminescence ..." *See* Abstract. Again, Nacamulli et al. do not disclose the claimed beads, or suggest such beads, because the reaction rate is determined by monitoring luminescence intensity in one type of reaction, between one type of reactant and one type of reaction partner, and that reaction produces the change in luminescence intensity of the group of reaction partners; *See, e.g.,* Abstract:

The reaction is conducted in an electrochemical cell with a mixture of reagents including a luminophore which will relate the concentration of a reactant, a reaction partner or the reaction product of a reaction partner to the ECL intensity. The reaction partner is a reagent which reacts with the reactant and which participates with the luminophore (or its reaction product participates with the luminophore) to cause the emission of ECL.

Accordingly, there is no reason provided by Nacamulli et al., with or without Gombinski, to make particles as set forth in independent claim 76 and thus, no motivation or suggestion to do so, and the rejection should be withdrawn.

The Examiner rejected claim 82 (should be claim 84) over Gombinski in view of Hugl et al., which relates to:

a sensor with a novel construction for a detection method of molecules labelled with fluorescent dye for detecting these dissolved substances or analytes by energy transfer with a simple fluorescence technique and increased sensitivity in the detection as well as versatile use for different tasks and the possibility of reproducible preparation of films bound to solid surfaces. [see Summary of the Invention]

As set forth in the Hugl et al. Summary of the Invention (col. 2, line 59 to col. 3, line 10), the optical biosensor is for monitoring of a single type of reaction based on fluorescence energy transfer:

- a) a solid support,
- b) a single-layer or multilayer Langmuir-Blodgett (LB) film attached to a),
- c) at least one fluorescent dye F_1 which is located in at least one of the top 4 layers of the LB film,
- d) a receptor molecule which is capable of specific interaction and which is bound or located in or on the topmost layer of the LB film, and
- e) a mobile fluorescent dye F_2 whose excitation band overlaps, sufficiently for an energy transfer, with the emission band of F_1 and which
 - e1) is covalently bonded to a ligand which is able to bind to the receptor, or which
 - e2) is covalently bonded to another receptor which is able to bind to the complex composed of the first receptor and ligand ...

Accordingly, there is no reason provided by Hugl et al., with or without Gombinski, to make particles as set forth in independent claim 76 and thus, no motivation or suggestion to do so, and the rejection should be withdrawn.

In conclusion, all claims are in condition for allowance and such action is requested.

Respectfully Submitted,

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